conditions are related, and tools which may be used in the two methods overlap. These facts have apparently obscured how distinct the two methods are.

The Patent and Trademark Office has officially held that the two methods are patentably distinct, and this holding must be honored as presumptively valid. See restriction requirement dated April 30, 1993 in Patent Application Serial No. 08/056,546, now Patent No. 5,492,808. (Tab 1.) In the restriction requirement, claims 1-10, directed to methods for detecting an FCC gene by detecting a linked polymorphic locus, were held separately patentable over claims 14-25, drawn to method of classifying a tumor as RER^+ or RER^-. Divisional applications were filed in reliance on the restriction requirement, eventually resulting in the issuance of Patent No. 5,871,925. Neither of these two patents is terminally disclaimed over the other.

The two methods are contrasted in the table below.

	Method 1	**Method 2**
Analyte	2p13 mutation	RER^+ (replication error phenotype)
Where found	any cell of the body	only in tumor tissue
How found	detecting a linked polymorphism	detecting microsatellite differences between tumor and normal tissue

de la Chapelle's Method 2 for analysis of RER is distinct from the claimed method of the subject application because de la Chapelle taught detection of RER^+ (microsatellite changes) in tumor tissue, whereas the method of the subject claims employs as a specimen body fluids which drain an organ having a cancer. de la Chapelle does not teach RER^+ detection in body fluids.

Examiner Souaya pointed out, however, that de la Chapelle Method 1 was also relevant. de la Chappelle teaches detection of linked polymorphisms to 2p13 mutations in blood (which is a body fluid); one of the types of polymorphisms which de la Chapelle teaches is a variable number of tandem repeat polymorphism (VNTR) which the Examiner asserted is essentially a microsatellite. (See column 5, line 1).

Even if, *arguendo,* VNTR were a microsatellite, as asserted by the Patent and Trademark Office, de la Chapelle still does not teach the invention. de la Chapelle teaches analysis of "a polymorphism which is linked to familial colon cancer (FCC)." Column 4, lines 61-62. This

polymorphism is not just any change found in microsatellite, but a particular marker that is constant in all cells of all affected family members. de la Chapelle teaches:

> In order to establish the genetic linkage or connection between the desired polymorphism and the FCC gene, it is necessary to analyze a set of familial relatives of the subject under investigation. The set is chosen so that it will allow determination of whether the FCC phenotype is linked to the presence of the polymorphism. Thus, preferably, several individuals are examined. These may include an unaffected parent, an affected parent, an affected sibling, an unaffected sibling, as well as other, perhaps more distant, members. Ideally, an unaffected parent, an affected parent and an affected sibling should be utilized. If an affected parent is deceased, satisfactory results can still be obtained if unambiguous segregation of the polymorphism with the FCC gene can be demonstrated in other members.
>
> For analysis using restriction fragment length polymorphism markers (RFLPs), blood (or other body tissue or sample containing DNA) is obtained from all individuals being studied, including the subject.

Column 5, lines 1-19. Thus the linked polymorphism of de la Chapelle is one which is fixed in the germline so that it is found in any and all cells of the person ("blood or other body tissue or sample containing DNA"). The polymorphism is one for which "unambiguous segregation . . . with the FCC gene can be demonstrated in other members."

In contrast, the method of claim 23 requires determination of a "microsatellite marker length alteration relative to a control sample" and that the test specimen is "of a body fluid which drains the organ" which is cancerous. de la Chapelle does not teach using a body fluid which drains the cancerous organ. de la Chapelle teaches using any body sample "blood or other body tissue or sample containing DNA." Further de la Chapelle does not teach "a microsatellite marker length alteration relative to a control sample." As shown at page 29 of the subject application, control samples are paired normal DNA to the tumor DNA. "These genetic alterations were identified as a novel band (or bands) in the tumor DNA lane and were not present in the paired normal DNA

lane." See also page 11, lines 8-10 ("the hypermutable nucleotide sequence is evidenced by nucleic acid deletions or expansion of repeat sequences as compared to a normal cell").

Thus the claimed method determines somatic mutations, *i.e.*, changes that occur in one somatic tissue but not in others. In contrast, Method 1 of de la Chapelle determines germline mutations which are present in all cells of the body. de la Chapelle fails to anticipate the method of claim 23 because de la Chapelle does not teach determining a microsatellite length alteration relative to a control sample, as that phrase is defined in the specification.

In summary, de la Chapelle teaches detection of germline mutations in blood or other body tissues (Method 1) and detection of somatic mutations in tumor tissue *per se* (Method 2). In contrast, claim 23 is directed to detecting somatic mutation in body fluids. Since de la Chapelle only teaches somatic mutations in tumor tissue *per se*, it does not anticipate the claimed methods of claim 23 or its dependents 24-26 and 28.

	de la Chapelle Method 1	**de la Chapelle Method 2**	**Sidransky Method**
Sample	blood or other body tissue or sample	tumor tissue	body fluid
Mutation detected	germline	somatic	somatic

Claims 27 and 39-34 are rejected as unpatentable over de la Chapelle, discussed above in view of Gonzalez-Zulueta, Merlo, and Ah-See. Claims 27 and 29-33 are dependent on claim 23, discussed above, and further recite a tetranucleotide repeat marker, head or neck cancer, lung cancer, bladder cancer, a urine sample, and a sputum sample, respectively. Gonzalez-Zulueta is cited as teaching tetranucleotide repeat marker instability in bladder and colorectal **cancers**; Merlo is cited as teaching microsatellite analysis in primary lung **tumors;** Ah-See is cited as teaching head and neck **tumors** with microsatellite instability.

As the Office Action correctly notes, none of the secondary references teaches use of a body fluid which drains an organ. Thus the secondary references are no different from de la Chapelle's Method 2, in which somatic microsatellite mutations are analyzed in tumor tissue. Thus the secondary references do not remedy the deficiency of the primary reference on its own.

None of the cited prior art teaches or suggests that somatic microsatellite mutations could be detected in body fluids that drain an organ bearing a tumor. None of the references suggests that somatic mutations occurring in tumors would be readily detectable in draining body fluids. This teaching is first disclosed in the subject application. It would not have been obvious that somatic microsatellite mutations would be readily detectable in body fluids, and none of the cited art suggests that it would have been. Body fluids may contain minute amounts of tumor cells as well as containing many other types of cells which are sloughed off. It would not have been clear that the signal of the microsatellite changes in tumor cells would be detectable among the background of other cells which do not contain such changes.

Claim 34 differs from claims 23-33 in reciting a specimen which is from a histopathological margin external to a primary tumor. No reference is cited by the Office Action as suggesting detection of microsatellite changes in such samples. Thus no *prima facie* case has been made.

Withdrawal of the two remaining rejections and of the finality of the Office Action is respectfully requested.

Respectfully submitted,

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By: _____
Sarah A. Kagan
Registration No. 32,141

BANNER & WITCOFF, LTD.
1001 G STREET, N.W., ELEVENTH FLOOR
WASHINGTON, D.C. 20001-4597
(202) 508-9100

SAK/ama